UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Review of Methamidophos Incident Reports
DP Barcode D258608, Chemical #101201

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BACKGROUND

The following data bases have been consulted for the poisoning incident data on the active ingredient Methamidophos (PC Code:101201):

1) OPP Incident Data System (IDS) - reports of incidents from various sources, including registrants, other federal and state health and environmental agencies and individual consumers, submitted to OPP since 1992. Reports submitted to the Incident Data System represent anecdotal reports or allegations only, unless otherwise stated. Typically no conclusions can be drawn implicating the pesticide as a cause of any of the reported health effects. Nevertheless, sometimes with enough cases and/or enough documentation risk mitigation measures may be suggested.

2) Poison Control Centers - as the result of Data-Call-Ins issued in 1993, OPP received Poison Control Center data covering the years 1985 through 1992 for 28 organophosphate and

carbamate chemicals. Most of the national Poison Control Centers (PCCs) participate in a national data collection system, the Toxic Exposure Surveillance System which obtains data from about 60-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc. In addition, as the result of a data purchase by EPA, OPP received Poison Control Center data covering the years 1993 through 1996 for all pesticides.

3) California Department of Pesticide Regulation - California has collected uniform data on suspected pesticide poisonings since 1982. Physicians are required, by statute, to report to their local health officer all occurrences of illness suspected of being related to exposure to pesticides. The majority of the incidents involve workers. Information on exposure (worker activity), type of illness (systemic, eye, skin, eye/skin and respiratory), likelihood of a causal relationship, and number of days off work and in the hospital are provided.

4) National Pesticide Telecommunications Network (NPTN) - NPTN is a toll-free information service supported by OPP. A ranking of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991, inclusive has been prepared. The total number of calls was tabulated for the categories human incidents, animal incidents, calls for information, and others.

METHAMIDOPHOS REVIEW

I. Incident Data System

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects unless otherwise noted.

Incident#960-1

A pesticide incident occurred in 1994, when an Italian man intentionally swallowed 45.6 grams of methamidophos in a 200 ml solution (estimated dose = 600 mg/kg) in a suicide attempt. He became comatose with cholinesterase level less than 10 percent of normal, which indicates a life-threatening poisoning. With treatment he recovered, however on day 25 weakness developed in his legs. Tests of nerve conduction velocities, evoked potentials, and neuro-toxic esterase confirmed a chronic case of peripheral neuropathy. Other such cases have been reported in the literature.

Incident#2195-4

A pesticide incident occurred in 1995 in California, when twenty-two field workers were weeding an alfalfa field that was treated the day before. Twelve workers experienced nausea and vomiting and sought medical care and two of the workers were admitted to the hospital for twenty-four hours. Enforcement action was taken for not properly posting the field to prevent worker entry. No further information on the disposition of the case was reported.

Incident#4158-1

A pesticide incident occurred in Idaho in 1996 when methamidophos drifted on to a garden. The owner of the garden was told not to eat the vegetables but entered the garden and was exposed by direct contact with the foliage. She was reportedly affected in a manner that persisted for 14 days. However, her symptoms were not reported. No further information on the disposition of this case was reported.

Incident#4215-9

A pesticide incident occurred in 1996, when the chemical got onto a thirty year old's skin and they experienced diarrhea, nausea, and headaches. No further information on the disposition of the case was reported.

Incident#4215-17

A pesticide incident occurred in 1996, when an individual inhaled the chemical and experienced headaches. No further information on the disposition of the case was reported.

Incident#6107-9

A pesticide incident occurred in 1997, when a thirty-eight year old individual experienced ocular irritation and pain. No further information on the disposition of the case was reported.

Incident#6532-4

A pesticide incident occurred in 1997, when an individual experienced agitation, irritation, and uncontrolled anger. No further information on the disposition of the case was reported.

Incident#6869-1

A pesticide incident occurred in 1997, when an aerial applicator applied methamidophos and chlorothalonil to a potato field and thirteen workers were exposed. As a result, one worker is claiming health problems and seeing a doctor daily, and another worker experienced coughing, green phlegm, headaches, and sinus problems. Neither victim reportedly had symptoms typical of organophosphate poisoning. No further information on the disposition of the case was reported.

Incident#7441-1

A pesticide incident occurred in 1998, when ten females were working on an apple field across the road from a potato field that was sprayed with methamidophos and several other chemicals. The workers experienced difficulty breathing, swelling of the tongue, nausea, headaches, vomiting, blurred vision, cough and respiratory irritation. Six of the workers were hospitalized for one night. No further information on the disposition of the case was reported.

Incident#7587-157

A pesticide incident occurred in 1996, when a twenty-two year old male experienced nausea, dizziness, weakness, and throat irritation after methamidophos and chlorothalonil were sprayed aerially about three hundred feet away. No further information on the disposition of the case was reported.

II. Poison Control Center Data - 1985 through 1992

Methamidophos was one of 28 chemicals for which Poison Control Center (PCC) data were requested. The following text and statistics are taken from an analysis of these data; see December 5, 1994 memorandum from Jerome Blondell to Joshua First.

The 28 chemicals were ranked using three types of measures: (A) number and percent occupational and non-occupational adult exposures reported to PCCs requiring treatment, hospitalization, displaying symptoms or serious life-threatening effects; (B) ratios of poisonings and hospitalization for PCC cases to estimated pounds reported in agriculture for pesticides used primarily in agriculture; and [C] number and percent of child exposures to PCCs requiring treatment, hospitalization, displaying symptoms or serious life-threatening effects.

A. Occupational and Non-occupational Exposure

From 1985-1992, there were a total of 121 methamidophos cases in the PCC data base. Of these, 41 cases were occupational exposure; 33 (80%) due to methamidophos alone and 8 (20%) involving exposure to multiple products including methamidophos. There were a total of 74 non-occupational exposures to adults and children six years old or older; 63 (85%) involving methamidophos alone and 11 (15%) with multiple products.

In this analysis, four measures of hazard were developed based on the Poison Control Center data, as listed below.

1. Percent of all accidental cases that were seen in or referred to a health care facility (HCF).

2. Percent of these cases (seen in or referred to HCF) that were admitted for medical care.

3. Percent of cases reporting symptoms based on just those cases where the medical outcome could be determined.

4. Percent of those cases with outcome determined that had a major medical outcome (defined as life-threatening or permanent disability) or death.

Exposure to methamidophos alone or in combination with other chemicals was evaluated for each of these categories, giving a total of 8 measures. A ranking of the 28 chemicals was done based on these measures with the lowest number being the most frequently implicated in adverse effects. Table 1 presents the analyses for occupational and non-occupational exposures.

Table 1. Measures of Risk From Occupational and Non-occupational Exposure to Methamidophos Using Poison Control Center Data from 1985-1992[a]

	Occupational Exposure	Non-occupational Exposure

Percent Seen in HCF		
Single product exposure	75.8 (68.2)	55.6 (44.0)
Multiple product exposure	80.5*[7] (69.8)	60.8 (46.1)
Percent Hospitalized		
Single product exposure	16.0 (12.2)	14.3 (9.9)
Multiple product exposure	24.2*[7] (14.3)	20.0*[6] (12.6)
Percent with Symptoms		
Single product exposure	95.0*[3] (85.8)	80.0 (74.0)
Multiple product exposure	96.2*[2] (85.8)	80.0 (75.2)
Percent with Life-threatening Symptoms		
Single product exposure	5.0*[2b] (0.0)	0.0 (0.0)
Multiple product exposure	3.8*[2b] (0.5)	0.0 (0.05)

a Extracted from Tables 2, 3, 5 and 6 in December 5, 1994 memo from Jerome Blondell to Joshua First; number in parentheses is median score for that category.
b The percents calculated for the occupational category are based on a single life-threatening case.
* Top 25% of chemicals are ranked with a superscript of 1 to 7.

Compared to other organophosphate and carbamate insecticides, methamidophos has a greater hazard in terms of percent developing symptoms, life-threatening symptoms (for the occupationally category only and based on a single case), and greater requirements for health care. In a combined ranking based on all four measures, methamidophos ranked second out of the 28 chemicals (mevinphos ranked first). Similarly, for the non-occupational category methamidophos ranked sixth out of 28 insecticides. The first or highest ranked insecticide was the one associated with the highest combined risk on the various measures.

B. Ratios of Poisoning - U.S. Poison Control Data

Active registrations of methamidophos are used primarily in agricultural settings. A comparison was computed for 15 pesticides with primary agricultural use between number of occupational exposures, poisonings, health care referrals and hospitalizations and the number of pounds active ingredient reported in use for 1989-1991. The results for methamidophos and the median for all 15 agricultural cholinesterase inhibitors included in the analysis are presented in the Table 2 below.

Table 2. Ratios of methamidophos exposures, poisonings, and cases referred to a health care facility (PCC Data, 1985-1992) to thousands of pounds active ingredient reported in use[a]

Pesticide	Exposure Per Use	Poisonings Per Use	Health Care Referral per Use	Hospitalizations Per Use
Methamidophos	.036	.022*[5]	.029	.007*[5]
Median	.033	.013	.027	.004

a Extracted from Table 9 in the December 5, 1994 memorandum from Jerome Blondell to Joshua First.
* Top 33% of chemicals are ranked with a superscript of 1 to 5

Among pesticides used principally in agricultural settings, methamidophos had higher ratios than other cholinesterase-inhibiting insecticides. The ratios of poisonings and hospitalizations per pounds active ingredient reported in use ranked fifth among the 15 insecticides that were compared (Table 2).

C. Exposure in Children

A separate analysis of the number of exposures in children five years of age and under from 1985-1992 was conducted. For methamidophos, there were 6 incidents; 5 involved exposure to methamidophos alone. Just one of these cases was seen in a health care facility. The number of cases was too small to warrant a more detailed evaluation.

Poison Control Center Data - 1993 through 1996

Results for the years 1993 through 1996 are presented below for occupational cases. Only 12 exposures were reported to be non-occupational in adults and older children, too few to warrant more detailed analysis. Of these 12 cases, six were seen in a health care facility, but none were hospitalized. Only three exposures were reported for children under age six, too few to warrant more extensive analysis. Unlike the earlier analysis for 1985-1992, cases involving exposures to multiple products are excluded. This is because the earlier analysis showed little difference in rankings and measurement of hazard when multiple exposure cases were included. Table 3 presents the occupational hazard information for methamidophos compared with all other pesticides on six measures: percent with symptoms, percent with moderate, major, or fatal outcome, percent with major or fatal outcome, percent of exposed cases seen in a health care facility, and percent hospitalized and percent seen in a critical care facility.
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Table 3. Comparison between methamidophos and all pesticides for percent cases with symptomatic outcome (SYM), moderate or more severe outcome (MOD), life-threatening or fatal outcome (LIFE-TH), seen in a health care facility (HCF), hospitalized (HOSP), or seen in an intensive care unit (ICU) reported to Poison Control Centers, 1993-1996 for occupational cases only.

Pesticide	SYM*	MOD*	LIFE-TH*	HCF*	HOSP*	ICU*
Methamidophos	90.0%	10.0%	0%	76.0%	10.5%	0%
All Pesticides	85.9%	18.8%	0.60%	46.8%	7.18%	2.89%

* Symptomatic cases based on those cases with a minor, moderate, major, or fatal medical outcome. Denominator for SYM, MOD, and LIFE-TH is the total cases where medical outcome was determined. Denominator for HCF is all exposures. Denominator for HOSP and ICU is all cases seen in a health care facility.

For occupational cases, methamidophos had only ten cases where outcome was determined. Therefore, differences in percents given in Table 3 are unlikely to be significant. Of 25 occupational exposures, 19 were seen in a health care facility and 2 of these cases required hospitalization. This suggests a higher requirement for health care but based on relatively few cases.

III. California Data - 1982 through 1994

Detailed descriptions of 158 cases submitted to the California Pesticide Illness Surveillance Program (1982-1994) were reviewed. In 71 of these cases, methamidophos was judged to be responsible for the health effects. Only cases with a definite, probable or possible relationship were reviewed. Methamidophos ranked 19th as a cause of systemic poisoning in California for this time period and 8th for cases involving only agricultural workers. Table 4 presents the types of illnesses reported by year. Table 5 gives the total number of workers that took time off work as a result of their illness and how many were hospitalized and for how long.

Table 4. Cases Due to Methamidophos Exposure in California Reported by Type of Illness and Year, 1982-1994

Year	Illness Type				
	Systemic[b]	Eye	Skin	Combination[c]	Total
1982	-	-	-	-	-
1983	6	-	1	-	7
1984	5	-	1	-	6
1985	3	-	-	-	3
1986	31	-	-	-	31
1987	-	-	-	-	-
1988	14	-	1	-	15
1989	1	-	-	-	1
1990	1	-	1	-	2
1991	2	-	-	-	2
1992	2	-	-	-	2
1993	-	-	-	-	-
1994	-	-	2	-	2
Total	65	-	6	-	71

[b] Category includes cases where skin, eye, or respiratory effects were also reported
[c] Category includes combined irritative effects to eye, skin, and respiratory system

Table 5. Number of Persons Disabled (taking time off work) or Hospitalized for Indicated Number of Days After Methamidophos Exposure in California, 1982-1994.

	Number of Persons Disabled	Number of Persons Hospitalized
One day	3	-
Two days	6	1
3-5 days	5	2
6-10 days	15	1
more than 10 days	11	-
Unknown	5	1

A total of 65 persons had systemic illnesses or 91.5% of 71 persons. A variety of worker activities were associated with exposure to methamidophos as illustrated in Table 6 below.

Table 6. Illnesses by Activity Categories for Methamidophos Exposure in California, 1982-1994

Activity Category	Illness Category				
	Systemic[b]	Eye	Skin	Combination[c]	Total
Applicator	1	-	-	-	1
Mixer/Loader	7	-	1	-	8
Drift exposure[a]	19	-	1	-	20
Field residue[a]	32	-	4	-	36
Commodity residue	2	-	-	-	2
Other	4	-	-	-	4
Total	65	-	6	-	71

[a] Drift exposure included 11 school instructors adjacent to a broccoli field being sprayed in 1988. Field residue included 25 workers in a cotton field that had been sprayed that morning.
[b] Category includes cases where skin, eye, or respiratory effects were also reported
[c] Category includes combined irritative effects to eye, skin, and respiratory system

According to the above activity categories, field residue was associated with the majority (51%) of the exposures. Twenty-five of the cases occurred after a cotton field was sprayed with methamidophos earlier in the morning. Drift exposure was also a problem with methamidophos,

accounting for 28% of the illnesses. The earlier 1994 review (December 5, 1994 memo from Jerome Blondell to Joshua First) found that methamidophos ranked highest for number of field workers poisoned (either by spray drift or field residue) per 1,000 applications from 1982 through 1989.

Weinbaum et al. (1997) analyzed risk factors for systemic illness in California for organophosphates for the time period 1984 through 1988. In their analysis they used the ratio of number of systemic illnesses to the pounds applied. Methamidophos was among five organophosphates that had statistically significant increased risk of poisoning. The estimated increase was 1.6 with a 95 percent confidence interval of 1.2 to 2.0. Only mevinphos, demeton, and oxydemeton-methyl had higher estimated ratios.

IV. National Pesticide Telecommunications Network

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, methamidophos was ranked 91st with 39 incidents in humans reported and 2 incidents in animals (mostly pets).

V. Literature

Rosenstock et al. (1991) performed a retrospective cohort study of agricultural workers in Nicaragua who had been hospitalized with organophosphate poisoning. Of 52 eligible patients hospitalized over a two year period, 38 men were located, and 36 agreed to participate in the study. Of the 36 who agreed to participate, 21 had been previously poisoned by methamidophos. Controls were a close male friend or sibling from the same community who had never been treated for pesticide poisoning and was no more than 5 years different in age from the case participant. Both members of the pair (case and control) were examined during May-June 1989 before the onset of the 4-5 month spraying season. Six of the seven tests from the World Health Organization core neurobehavioral test battery were administered, along with a brief symptom inventory, 6 additional Spanish-translated tests, and a 16 item self-reported symptom inventory. These tests were administered an average of 2 years after the time of hospitalization for poisoning.

Poisoned workers scored significantly worse on five of the six WHO core neurobehavioral tests, 3 of the 6 Spanish-translated tests, and the 16 item self-reported inventory. Deficits were noted in auditory and visual attention, visual memory, visuomotor skills, steadiness and dexterity. These findings replicated, to a large degree, those of Savage et al., which is an important consideration when judging the weight of evidence for a conclusion that OP poisoning is a cause of chronic neurobehavioral effects.

McConnell et al. (1994) evaluated vibration threshold in 36 Nicaraguan workers poisoned by organophosphate insecticides (the same cohort studied by Rosenstock et al. above). All of the

workers had been poisoned and hospitalized from one to three years prior to this study. Of the 36 workers, 21 had been poisoned by methamidophos. The group poisoned by methamidophos had higher mean vibration thresholds than those (n = 15) poisoned by other organophosphates who also had higher mean thresholds than the unexposed control group (each exposed case was matched to a sibling or friend with the same sex and age within five years). These differences were largest in the lower extremities. Testing for suspected confounders (e.g., recent pesticide exposure, history of solvent exposure, and history of work with vibrating machinery) did not alter these results. The authors concluded "These results strongly suggest a chronic sensory impairment resulting from methamidophos poisoning."

Karalliedde et al. (1988) reported on a 22 year old pregnant woman who ingested methamidophos with suicidal intent. It was estimated that she was 36 weeks pregnant at the time. She had severe poisoning and received treatment three hours after the ingestion, including atropine, pralidoxime, and required mechanical ventilation for six days. Forty-four days after the intoxication she delivered a healthy boy with a birth weight of 2.85 kg (6.2 pounds). The authors attribute the healthy baby to prompt and adequate management of the life-threatening phases of the poisoning.

McConnell and Hruska (1993) reported on an epidemic of 548 pesticide poisonings in northwestern Nicaragua during June and July 1987. Of the 548 cases, 91% were occupational, 8% involved other accidents, and 1% were suicide attempts. Of the occupational cases, one-third were due to methamidophos.

Senanyake and Johnson (1982) reported on 10 cases of severe poisoning to methamidophos that developed polyneuropathy about two to four weeks later. All of the cases occurred in Sri Lanka and were unconscious upon admission to the hospital with signs of severe anticholinesterase poisoning. Seven of the 10 cases were suicide attempts. In the other three cases: one spilled the product on his body while opening the bottle; another was poisoned from dermal and inhalation exposure by spraying; and the third accidently ingested the product while sucking on a tube from the spraying machine.

Senanayake and Karalliedde (1987) reported on a life-threatening sequelae to organophosphate poisoning which they referred to as an intermediate syndrome. They observed 10 patients that had paralysis of the proximal limb muscles , neck flexors, motor cranial nerves, and respiratory muscles 1-3 days after poisoning. One of the ten patients was poisoned by methamidophos (suicide attempt) and required mechanical ventilation. The weakness persisted for 32 days which overlapped the development of a delayed polyneuropathy. In an earlier report of a series of 27 patients with delayed neuropathy (Senanayake, Journal of Neurology 232: Suppl. page 203, abstract, 1985), 25 were caused by methamidophos.

Sun et al (1998) reported that methamidophos was responsible for half of the pesticide intoxications and fatality cases in China. A total of 553 intoxications due to dermal exposure to methamidophos and 104 cases by ingestion were reported from 1987 through 1992 among 5 hospitals in rural China. They reviewed the medical records of 104 subjects that had been

poisoned by ingestion (mostly attempted suicides) and performed in-person interviews and medical examinations with 100 of these subjects and interviewed relatives of the remaining four. Among the 104 cases, 14 cases of organophosphate-induced delayed polyneuropathy (OPIDP) were identified. Six of the 14 cases had ingested a mixture of methamidophos and dimethoate. In 13 of the 14 OPIDP cases, the initial poisoning was severe (12 cases exhibited coma and 3 suffered from urine and feces incontinence). All 14 cases were confirmed by severely inhibited blood cholinesterase. All 14 OPIDP cases complained of paralysis and reeling gait. Most OPIDP cases recovered within two years of their intoxication.

Goh et al. (1990) reported on an outbreak of food poisoning in Singapore which occurred in 1988. A total of 105 cases of illness among those who had consumed gai-lan vegetables were treated at hospitals during the December 3-7 period. Among 68 cases examined at one of the hospitals, 98% exhibited vomiting, 67% reported abdominal cramps, 65% diarrhea, 37% nausea, 63% giddiness, 31% excessive sweating, 30% blurred vision, 19% headache, and 12% muscle twitching. Testing of the suspected vegetables identified 2.4-31.7 ppm methamidophos, 1.1-5.4 ppm profenofos, and 4.1-16.8 ppm dithiocarbamate fungicide. The authors noted "the higher acute toxicity of methamidophos, together with its 5 times higher level of residue detected in the vegetable, would evidence that methamidophos was mainly responsible for the poisoning." The authors go on to estimate the total ingestion by assuming 10% of the highest combined level of methamidophos and profenofos residues remained after cooking and washing and that the average person eats 150 grams, giving an ingestion of 0.56 mg per person. Blood cholinesterase levels were depressed 26-81% below normal in five of the hospitalized patients who were tested.

Chan et al. (1996) reported there were 47 outbreaks of food poisoning in Hong Kong in 1992, all of which were caused by methamidophos. An estimated 329 people were affected. The authors estimated that these food-borne poisonings exceeded the incidence of pesticide poisonings that were not related to dietary intake by five-fold.

VI. Conclusions

Based on Poison Control Center data for 1985 through 1992, methamidophos ranked second out of 28 cholinesterase-inhibiting insecticides on combined measures of hazard. Similarly for non-occupational cases (typically bystanders or other workers not directly involved in application), methamidophos ranked sixth. An earlier review of California data found that methamidophos had the highest risk of field worker poisoning per 1,000 applications but that this was influenced by large clusters. For example, in one incident 25 workers were poisoned in a cotton field that had been treated that morning, a clear violation of the required reentry waiting period. Overall combining California and Poison Control Center data rankings, led to methamidophos being ranked third (after mevinphos and carbofuran) for combined measures of hazard.

Residues of methamidophos have been a significant source of poisoning whether for field workers tending treated crops (as described above) or unacceptable residues left of foods which have been reported largely in Asian countries.

Organophosphate-induced delayed neuropathy in seriously poisoned cases, intermediate syndrome, and chronic neurobehavioral effects have been directly linked to poisoning from methamidophos.

VII. Recommendations

Methamidophos probably poses one of the highest risks to workers of any organophosphate insecticide currently registered. Significant reductions in hazard to workers would result from cancellation of most uses. Where safer alternatives are not available, a full set of restrictive measures including posting, closed-mixing loading, reentry restrictions, and buffer zones to prevent drift to nearby workers or residential areas should be instituted. Special efforts are needed to assure that reentry intervals and pre-harvest intervals are observed to prevent poisonings from residue. A requirement on all remaining methamidophos products should require mandatory reporting of any adverse effects to a telephone number provided on the label.

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